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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/421,422	HARBURY ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-10, 15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

JON EPPERSON
PRIMARY EXAMINER

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/6/07 has been entered.

Claim Status

2. Claims 2 and 11-14 have been cancelled.

Claims 1, 3-10, 15 and 16 are currently pending.

Claims 1, 3-10, 15 and 16 are being examined in this application.

Election/Restrictions

3. Applicant's election of Group I invention (original claims 1-10) of a method of synthesizing a plurality of compounds, in the Reply, filed on 3/26/2001, is as previous acknowledged.

Priority

4. This application claims priority to U.S. Provisional Patent Application Nos. 60/104,744, filed 10/19/1998.

Claim Rejections Withdrawn

5. Upon further consideration, the following claim rejections are withdrawn:

A) Claims 1, 3-10, 15, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

However, new rejections under 35 U.S.C. 112, first paragraph are formulated. See the subsequent rejections in the instant Office action.

Applicants argument against the above said withdrawn claim rejections are moot.

B.) Claims 1, 3-10, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

However, new rejections under 35 U.S.C. 112, second paragraph are formulated. See the subsequent rejections in the instant Office action.

Applicants argument against the above said withdrawn claim rejections are moot.

New Claim Objections / Rejections

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

7. Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite a method of tag-directed synthesis of a plurality of compounds, comprising: (a) forming a first group of subsets of nucleic acid tags for participating in a first synthetic reaction step from a pool of nucleic acid tags, wherein each nucleic acid tag comprises a first hybridization sequence linked to a second hybridization sequence, which said second hybridization sequence is linked to a chemical reaction site, by contacting said nucleic acid tags with a plurality of first immobilized nucleotide sequences, each designed to capture a subset of said nucleic acid tags by hybridization between one of said first hybridization sequences and the first immobilized sequence;

(b) carrying out the first synthetic step by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in (a) with a selected one of a plurality of first reagents to convert the chemical reaction site of each subset of nucleic acid tag to a reagent-specific compound intermediate to produce subsets of reacted nucleic acid tags;

(c) pooling the subsets of reacted nucleic acid tags;

(d) forming a second group of subsets of the pooled reacted nucleic acid tags of step (c), for participation in a second synthetic reaction step, by contacting said pooled reacted nucleic acid tags with a plurality of second immobilized nucleotide sequences, each designed to capture a subset of said reacted nucleic acid tags by hybridization between one of said second hybridization sequences and the second immobilized sequence; and

(e) carrying out the second synthetic step by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in (d) with a selected one of a plurality of second reagents.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to consider the decision of the Court of Appeals for the Federal Circuit, which holds that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

The instant claims are drawn to a genus of methods comprising various steps and reagents. Claim 1 recites a genus of methods requiring a genus of "nucleic acid tags", a genus of "chemical reaction sites", a genus of "reactions" or "synthetic steps", and a genus of "reagents". Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genuses of "reagents" (or compounds), "nucleic acids", "reactions".

Thus, the claims are drawn to any nucleic acid molecules, any chemical reaction sites (or any compounds), any chemical reactions, etc. In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genuses.

In general, the instant claims are drawn to combinatorial synthesis methods using nucleic acid molecules as tags (through hybridization) for selection of the chemically (or enzymatically) formed products.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. (see MPEP 2163 II).

In this case, the instant application defines the term "nucleic acid tag" as "the nucleotide acid sequences which comprise a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site" (p. 9, para 4), which encompasses any nucleic acid molecule.

The instant specification defines the term "chemical reaction site" as "a chemical component capable of forming a variety of chemical bonds including, but not limited to ..." (p. 9, para 3), which essentially encompasses any chemical entity that can form bonds.

The instant specification is general and prophetic in nature, and does not provide any specific examples of the claimed genus of nucleic acid molecules, chemical reactions, and chemical reagents that are capable of being used with the claimed method. In particular, the specification does not demonstrate what specific nucleic acid sequences are capable of forming

the "nucleic acid tags" that would hybridize for the selection steps, and also allowing the chemical reactions to proceed.

It is known in the art that certain chemical reactions would destroy the integrity of nucleic acid molecules. For example, Greene et al (Protective Groups in Organic Synthesis. 3rd ed. NY. 4/1999; p.v, pp. 1-5, p. 502-503 only) teaches "when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked" (p. 1, lines 1+). Greene et al also teach the protection of the nitrogen bases including adenine, cytosine, etc. are needed (p. 502, last para). Thus, in chemical synthesis such as generation of oligonucleotides (i.e. addition of nucleotides to a nucleic acid strand), protection groups of the "multifunctional compounds" (such as nucleic acids) are needed to protect the integrity of the generated nucleic acids. The instant specification does not provide any guidance to the reaction condition under which the "first" and "second" or any subsequent "synthesis steps" are carried out. It is not shown how the integrity of the nucleic acids would be preserved for conducting subsequent or concurrent hybridization reactions. Furthermore, even with the appropriate protection groups such as carbamates formed on the nucleotide bases, problems such as interference with proper base pairing during hybridization reaction would still exist.

The instant claims also encompass attaching the "chemical reaction site" anywhere on the "nucleic acid tags". For example, a reaction moiety (such as a small organic molecule) can be attached at the middle of the hybridization sequences. It may be likely that the reaction moiety would interfere with the hybridization reaction (e.g. attachment onto the nucleotide base), or the formed hybridization complex may interfere with the chemical reaction.

In addition, the instant claims recite "nucleic acid tags" without specifying if the nucleic acid molecules are single stranded or double stranded. In certain method steps (e.g. Claim 10), the steps require nucleic acids to be in the double stranded form for the claimed "restriction" digestion to proceed, because "restriction enzymes" recognizes double stranded nucleic acid molecules. However, throughout the instant claims (e.g. Claim 1), the "nucleic acid tags" seem to be in single stranded forms, because the "nucleic acid tags" are hybridized to the "immobilized nucleotide sequence". Thus, for "nucleic acid tags" in the single stranded form, the instant specification has not shown possession of the method of "restriction digestion". For double stranded "nucleic acid tags", the instant specification has not shown possession of how the hybridization steps can occur.

The above only illustrates a few examples of how unpredictable the method of using nucleic acid molecules as tags to select or make chemical products through the entities attached to the nucleic acid tags. The instant disclosure does not provide any structural limitation or representative species to show possession of the claimed entire genus of methods that use different reagents/compounds and steps.

Therefore, applicants are not in possession of the entire claimed methods using the claimed entire genuses of "nucleic acid tags", "chemical reaction sites", "reagents", and "synthetic steps". Applicant's claimed scope represents only an invitation to experiment regarding possible chemical reactions that can be preformed to possible chemical entities attached to possible nucleic acid tags.

Scope of Enablement Rejection

8. Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using certain nucleic acids as tags for selecting certain reaction products (attached to the nucleic acid tags), does not reasonably provide enablement for using any other nucleic acid molecules to generate any chemical entities attached thereon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims / The nature of the invention

The nature of the instant invention is a method of generating various reaction products using various reactive entities linked to various nucleic acid tags, which can be selected using immobilized complementary nucleic acids through hybridization reaction.

The breadth of the claims seems to encompass various steps and reagents. Claim 1 recites a genus of methods requiring a genus of "nucleic acid tags", a genus of "chemical reaction sites", a genus of "reactions" or "synthetic steps", and a genus of "reagents". Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genuses of "reagents" (or compounds), "nucleic acids", "reactions". Thus, the claims are drawn to any nucleic acid molecules, any chemical reaction sites (or any compounds), any chemical reactions, etc. In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genuses.

The state of the prior art / The predictability or lack thereof in the art

It is known in the art that certain chemical reactions would destroy the integrity of nucleic acid molecules. For example, Greene et al (Protective Groups in Organic Synthesis. 3rd ed. NY. 4/1999; p.v, pp. 1-5, p. 502-503 only) teaches "when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked" (p. 1, lines 1+). Greene et al also teach the protection of the nitrogen bases including adenine, cytosine, etc. are needed (p. 502, last para). Thus, in chemical synthesis such as generation of oligonucleotides (i.e. addition of nucleotides to a nucleic acid strand), protection groups of the "multifunctional compounds" (such as nucleic acids) are needed to protect the integrity of the generated nucleic acids. The instant specification does not provide any guidance to the reaction condition under which the "first" and "second" or any subsequent "synthesis steps" are carried out. It is not shown how the integrity of the nucleic acids would be preserved for conducting subsequent or concurrent hybridization reactions. Furthermore, even with the

appropriate protection groups such as carbamates formed on the nucleotide bases, problems such as interference with proper base pairing during hybridization reaction would still exist.

The instant claims also encompass attaching the "chemical reaction site" anywhere on the "nucleic acid tags". For example, a reaction moiety (such as a small organic molecule) can be attached at the middle of the hybridization sequences. It may be likely that the reaction moiety would interfere with the hybridization reaction (e.g. attachment onto the nucleotide base), or the formed hybridization complex may interfere with the chemical reaction.

In addition, the instant claims recite "nucleic acid tags" without specifying if the nucleic acid molecules are single stranded or double stranded. In certain method steps (e.g. Claim 10), the method requires nucleic acids to be in the double stranded form for the claimed "restriction" digestion to proceed, because "restriction enzymes" recognizes double stranded nucleic acid molecules. However, throughout the instant claims (e.g. Claim 1), the "nucleic acid tags" seem to be in single stranded forms, because the "nucleic acid tags" are hybridized to the "immobilized nucleotide sequence". Thus, for "nucleic acid tags" in the single stranded form, the instant specification has not shown possession of the method of "restriction digestion". For double stranded "nucleic acid tags", the instant specification has not shown possession of how the hybridization steps can occur.

The above only illustrate a few examples of how unpredictable the method of using nucleic acid molecules as tags to select or make chemical products through the entities attached to the nucleic acid tags. The instant disclosure also does not provide any structural limitation or representative species to show possession of the claimed entire genus of methods that use different reagents/compounds and steps. Although there may be suggested methods of

overcoming these problems through non-routine experimentations, there are no predictable methods or solutions that would solve all the problems for any nucleic acid tags, any chemical reaction, any reaction agents, etc.

The level of one of ordinary skill

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction or guidance present / The presence or absence of working examples

The instant specification is general and prophetic in nature, and does not provide any specific examples of the claimed genus of nucleic acid molecules, chemical reactions, and chemical reagents that are capable of being used with the claimed method. In particular, the specification does not demonstrate what specific nucleic acid sequences are capable of forming the "nucleic acid tags" that would hybridize for the selection steps, and also allowing the chemical reactions to proceed. The instant specification also does not provide any working examples of a chemical synthesis step performed on the claimed nucleic acid tags.

The quantity of experimentation needed

Due to the unpredictabilities of various chemical reactions performed on nucleic acid tags (and/or its linked chemical reaction sites) and the effects of the chemical reactions on the hybridization of the nucleic acid tags, undue experimentation would be required. The art has not demonstrated all the possible nucleic acid tags and all possible chemical reactions that are compatible with the linked nucleic acid tags. Because the instant specification does not provide

any specific guidance on how various chemical reactions can be conducted without destroying the integrity of the nucleic acid tags and other problems associated with the claimed method, undue experimentation would be required to practice claimed method of synthesizing any chemical compound using any linking nucleic acid tags.

Conclusion

Due to the non-routine experimentation necessary to determine the specific methods for conducting chemical synthesis using chemical reaction sites linked to nucleic acid tags while allowing specific hybridization to occur prior, during or subsequent to the chemical reactions; the lack of direction/guidance presented in the specification regarding the specific requirements for the method; the unpredictability of various chemical syntheses using compounds with multifunctional groups (such as nucleic acids) as established by the state of the prior art; the breadth of the claims, undue experimentation would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

Second paragraph of 35 U.S.C. 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A.) Claim 1 method recites the method step of "(a) forming a first group of subsets of nucleic acid tags ... by hybridization between one of said first hybridization sequences and the first immobilized sequences", which can be interpreted to mean that hybridization complexes have been formed between the tags and the immobilized nucleic acids. The claim also recites a step "(b) carrying out the first synthetic step ... of the subsets formed in (a)", which can be broadly interpreted to mean the reactions are conducted using the hybridization complexes formed in step (a) of Claim 1. That is the hybridization complexes are maintained while allowing the chemical reaction to occur. However, applicants in the Reply (entered 12/4/06; p. 7) seem to argue that claim should be interpreted to mean that the hybridization complexes occur at different time from the chemical reactions. Applicants' narrow interpretation seems to be in conflict with the broad and reasonable interpretation of the instant claim language. Thus, applicants invention are not clearly described by the instant claim language. One of skill in the art would not be able to define the metes and bounds of the instant claimed invention.

B.) Claim 5 recites the limitation "the compound intermediates" in step (g). There is insufficient antecedent basis for this limitation in the claim.

C.) Claim 16 recites the limitation "the separate subset" in line 2. There is insufficient antecedent basis for this limitation in the claim.

D.) Claim 9 recites "wherein said using includes", which the term said using is not clear. It is not clear if claim 9 is reciting a subsequent method step following the method steps recited in Claim 8, or if claim 9 is further limiting the method steps recited in Claim 8.

E.) Claim 10 recites the limitation "said plurality of compounds" in step (f). There is insufficient antecedent basis for this limitation in the claim. It is not clear to which one of the

"compounds" recited in the preamble of Claim 10, the compound intermediate of Claim 1, and the final compounds formed in Claim 1.

F.) The claim language of 10 is convoluted and confusing. It is not clear if the recited method steps (f)-(i) are further limiting the recitation of Claim 7 or the steps are further method steps comprised by the method of claim 1.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(Note: the instant claim numbers are in bold font.)

5,635,400

12. Claims 1, 3-8, 10, 15 and 16 are rejected under **35 U.S.C. 102(b)** as being anticipated by Brenner (US 5,635,400; 6/3/1997).

The instant claims recite "a method of tag-directed synthesis of a plurality of compounds, comprising: (a) forming a first group of subsets of nucleic acid tags for participating in a first synthetic reaction step from a pool of nucleic acid tags, wherein each nucleic acid tag comprises a first hybridization sequence linked to a second hybridization sequence, which said second hybridization sequence is linked to a chemical reaction site, by contacting said nucleic acid tags with a plurality of first immobilized nucleotide sequences, each designed to capture a subset of said nucleic acid tags by hybridization between one of said first hybridization sequences and the first immobilized sequence;

(b) carrying out the first synthetic step by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in (a) with a selected one of a plurality of first reagents to convert the chemical reaction site of each subset of nucleic acid tag to a reagent-specific compound intermediate to produce subsets of reacted nucleic acid tags;

(c) pooling the subsets of reacted nucleic acid tags;

(d) forming a second group of subsets of the pooled reacted nucleic acid tags of step (c), for participation in a second synthetic reaction step, by contacting said pooled reacted nucleic acid tags with a plurality of second immobilized nucleotide sequences, each designed to capture a subset of said reacted nucleic acid tags by hybridization between one of said second hybridization sequences and the second immobilized sequence; and

(e) carrying out the second synthetic step by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in (d) with a selected one of a plurality of second reagents."

Brenner, throughout the patent, teaches using various methods of using oligonucleotide tags.

The reference teaches generating a variety of oligonucleotide tags with attached "reactive functionalities (e.g. col. 9, lines 15+) and various hybridization sequences (e.g. col. 6+), which read on the "nucleic acid tags" linked to a chemical reaction site of **clm 1**.

The reference teaches hybridizing the "oligonucleotide tags" to a solid support through its complementary hybridization sequences (e.g. col. 12, lines 15+; Figure 4, where the solid support (245) has immobilized hybridization nucleotide sequences (250) that are complimentary to the olignucleotide tags (255)), which reads on the **(a) of clm 1**, and the solid support of **clm 15**.

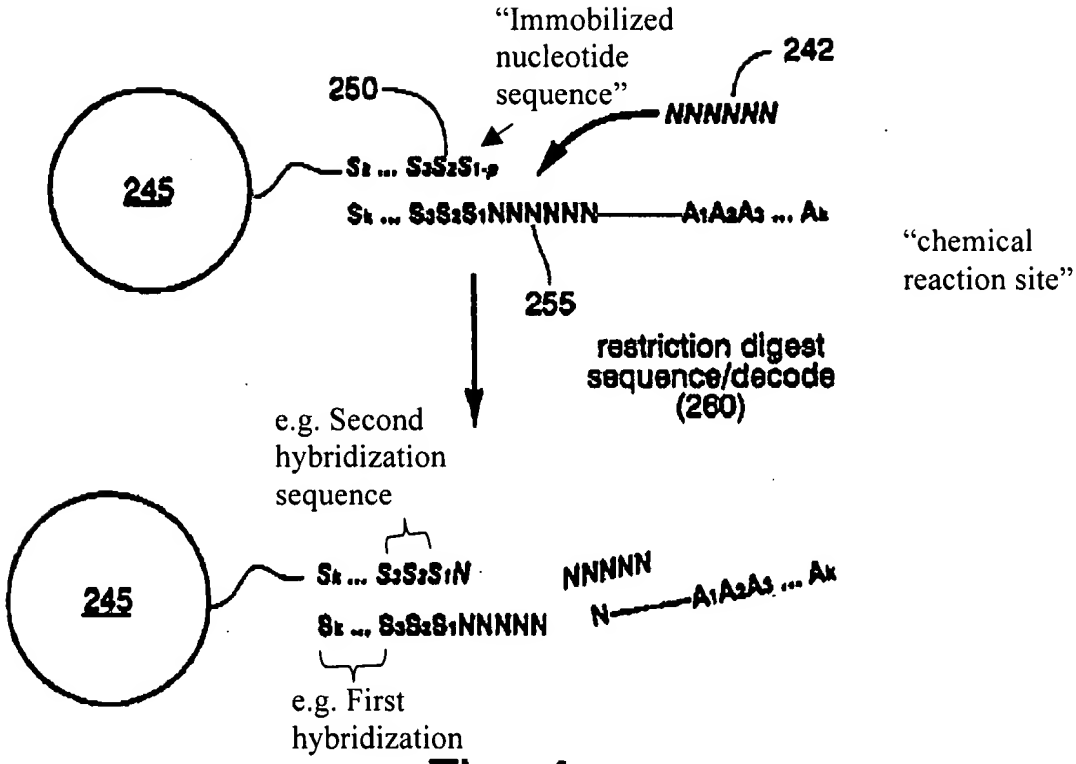

Fig. 4

The reference also teaches attaching various moieties to the end of the oligonucleotide tags (e.g. col. 9) through chemical reactions such as synthesizing labeled peptides (e.g. cols. 11-12; top of Figure 4), and restriction digestion of the hybridized oligonucleotide tags (e.g. col. 12, lines 15+), which either the chemical reactions or the restriction digestion reads on **(b) of clm 1**.

The reference teaches sorting the oligonucleotides (e.g. col. 12, lines 10+), which reads on **(c) of clm 1**.

As indicated in Figure 4 cited above, the reference also teaches a second hybridization sequence that are hybridized to the a second immobilized nucleotide sequence (e.g. Figure 4), which reads on **(d) of clm 1**.

The reference also teaches ligating another nucleotide sequence to the restricted oligonucleotide tag during the "single base DNA sequencing" procedure (e.g. cols. 16-17; especially, col. 16, lines 65+; Figures 1 and 2), which reads on **(e) of clm 1**.

The "restriction" and "ligation" reactions taught by the reference either cuts or adds nucleotides to the oligonucleotide tags (or nucleic acid tags), which reads on the "different oligomer subunits" of **clm 3**, as well as the "different compound substituents" of **clm 4**.

The reference also teaches repeating the ligation, restriction cleaving, identifying, etc., (reads on the hybridization and the synthetic step discussed above) for as many times as necessary (e.g. col. 17, lines 4+), which reads on the "N" synthetic steps of **clm 5**, the iterative step of **clm 8**, and the method steps of **clm 10**.

The reference teaches each oligonucleotide tag has different subset of sequences (e.g. Figure 4; cols. 6-7+), and each of the ligation step during the "single base DNA sequencing" also produce different sequences for the oligonucleotide tags (e.g. col. 17-18), which reads on the at least 5 separate hybridization sequences of **clm 6**.

The reference teaches a restriction site in the oligonucleotide tags (e.g. Figure 4, the "NNNNN" region; col. 11, lines 60+), and the oligoncleotides having "sets" of sequence that are the same (e.g. col. 6, lines 30+), which reads on the "spacer sequence" of **clm 7**, and the restriction sites of **clm 10**.

The reference teaches sorting the oligonucleotide tags into tubes, or other solid substrate (e.g. cols. 19-20), which reads on the limitation of **clm 16**.

WO93/21340

13. Claims 1, 3-8, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenthal et al (WO9321340; 10/28/1993).

Rosenthal et al, throughout the publication, teach using immobilized template and template specific primer for DNA sequencing reaction (Abstract).

The reference teaches immobilizing single-stranded template (nucleic acids) to solid-phase support (pp. 7-8), which reads on the "immobilized nucleotide sequence" of step (a) of **clm 1**, as well as **clm 15**

The reference teaches hybridizing a "primer" to the immobilized template (p. 7, lines, 7+ and 25+), which the primer reads on the "nucleic acid tag" of **clm 1**.

The reference teaches "extending the primer by the addition of a single labeled nucleotides (p. 7, lines 10+), which reads on the "first synthetic step" of **clm 1**.

The primers and the templates taught by the reference comprise at least "a first hybridization sequence" (partial sequence of the primer or the template) and "a second hybridization sequence" (partial sequence of the primer or the template), as recited in **clm 1**. The primers would also possess at least five partial sequences, which reads on the 5 separate hybridization sequences of **clm 6**, as well as the same spacer regions of **clm 7** (see also p. 24, Example 1).

The primers are used in one sequencing reaction described by the reference (p. 7) would "pooled" as recite din step (c) of **clm 1**.

The reference teaches repeating the extension steps of the sequence reaction while the primers are hybridized to the template (p. 7), which reads on the second hybridization step and the second synthetic reaction step of **clm 1**, as well as the N synthetic steps of **clm 5**.

The reference teaches adding different nucleotides to the primers (pp. 11-12), which reads on the different oligomer subunits of **clm 3**, as well as the different compound substituents of **clm 4**.

The reference teaches identifying the sequence of the extended primer based on the different labels (p. 7, lines 14+), which reads on identifying a subpopulation of **clm 8** because only the right primer-template complex can produce a primer extension product.

Because the sequencing reactions are carried out in test tubes (pp. 23-24), the reference's teaching reads on the limitation of **clm 16**.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

'400 and '598

15. Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brenner (US 5,635,400; 6/3/1997), in view of Lerner et al (US 5,723,598; 3/3/1998; filing date: 6/18/1996).

Brenner, throughout the patent, teaches using various methods of using oligonucleotide tags, as discussed above.

Brenner et al do not explicitly using PCR to amplify the nucleic acid tags, as recited in **clm 9**.

However, Lerner et al, teach using PCR to amplify nucleic acids. The reference teaches amplification of selected DNA using PCR (col. 2, lines 22+). The reference also teaches the advantage of PCR such as allowing "serial enrichment" and subsequent sequencing step of the PCR products (col. 2, lines 22+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to amplify the selected nucleic acid tags using PCR.

A person of ordinary skill in the art would have been motivated at the time of the invention to use PCR to amplify the selected nucleic acid tags, because the advantage of the PCR technology such as allowing serial enrichment of the nucleic acid molecule and subsequent sequencing step, as taught by Lerner et al.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications, because the using PCR to amplify nucleic acid molecules is routine and known in the art as taught by both Brenner et al (col. 2, lines 22+), and Lerner et al.

WO and '097

16. Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal et al (WO9321340; 10/28/1993), in view of Lerner et al (US 5,723,598; 3/3/1998; filing date: 6/18/1996; cited in IDS) and Brenner (US 5,635,400; 6/3/1997).

Rosenthal et al, throughout the publication, teach using immobilized template and template specific primer for DNA sequencing reaction, as discussed above.

Rosenthal et al do not explicitly using PCR to amplify the nucleic acid tags, as recited in **clm 9**. The reference also does not explicitly teach using restriction enzymes to cut the nucleic acid tags, as recited in **clm 10**.

However, Lerner et al, teach using PCR to amplify nucleic acids. The reference teaches amplification of selected DNA using PCR (col. 2, lines 22+). The reference also teaches the advantage of PCR such as allowing "serial enrichment" and subsequent sequencing step of the PCR products (col. 2, lines 22+).

Brenner et al, teach repeating restriction cleaving and ligation (e.g. col. 17, lines 4+), and a restriction site in the oligonucleotide tags (e.g. Figure 4, the "NNNNN" region; col. 11, lines 60+). The Brenner reference also teaches the need to engineer a restriction site in the nucleic acid tag such as the need to release the nucleic acid tag for subsequent reactions (col. 10, lines 6+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to amplify the selected nucleic acid tags using PCR and to engineer a restriction site for repeating restriction and ligation steps.

A person of ordinary skill in the art would have been motivated at the time of the invention to use PCR to amplify the selected nucleic acid tags, because the advantage of the PCR

technology such as allowing serial enrichment of the nucleic acid molecule and subsequent sequencing step, as taught by Lerner et al.

A person of ordinary skill in the art would have been motivated at the time of the invention to engineer a restriction site in the nucleic acid tags for subsequent cleaving and ligation reactions, because the need for releasing the nucleic acid tags for subsequent reactions, as taught by Brenner et al.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications, because the using PCR to amplify nucleic acid molecules, and engineering restriction sites (or cleaving by restriction enzyme) are routine and known in the art as taught by Rosenthal et al, Lerner et al, and Brenner et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1639
5/11/07

JON EPPERSON
PRIMARY EXAMINER